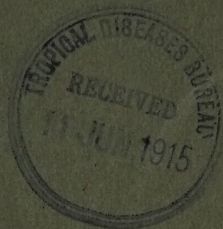


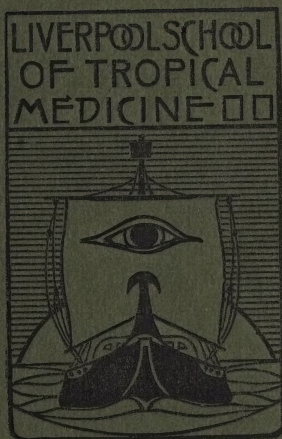
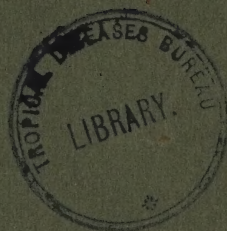
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Dengue

BY
HARALD SEIDELIN



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DENGUE

A Summary

BY HARALD SEIDELIN.

*Synonyms.**—Dengue fever, dandy fever, broken wing, break-bone fever, break-heart fever, eruptive articular fever, eruptive rheumatic fever, stiff neck fever, pantomime fever, three-day fever (not Pappataci fever), perhaps six-day fever, seven-day fever (perhaps including Rogers's), bilious remittent fever, red fever, fièvre articulaire exanthématique, fièvre entéro-rhumatismale, fièvre articulaire des pays chauds, fièvre exotique rouge, fièvre chinoise, fièvre des dattes, mal des genoux, bouquet, Dengelfieber, Knieübel, daggeïsche Fieber, rheumatische Influenza, knokkelkoorts, Semarangsche koorts, febris polka, scarlatina rheumatica, roseola rheumatica, exanthesis rosalia, exanthesis arthrosis, trancazo, calentura roja, giraffe, plantaria, gaditana, zamparina, andancio, boubou, abudobus, baridixabis, homa mguu, abu ndefu, kidinga pépo, muda mariata, aburabaka, bonon toohutia, dunga, abu rokab, ridagamonté, n'rogai, influenza rusa, tootia, bonon, abou rekabe, or abu rikab.

The word dengue means, in Spanish, affectation, and corresponds thus very well to many of the other names which have, in various languages, been given to the disease. The natural explanation of the term seems, therefore, to be that it has been introduced into other languages from Spanish, which transition would very easily have taken place, considering that Spain was the first country in Europe in which dengue was observed. It is, however, maintained by some authorities that the word is of Arabic, Indian, or East African origin.

Definition. Dengue is an acute febrile disease of short duration and of comparatively benign character, produced by a parasite which is probably an inhabitant of the blood, and transmitted from one individual to another by a mosquito.

This definition is vague, and does not sufficiently

* Chiefly after van der Burg: Das Dengue-Fieber, in Mense's 'Handbuch der Tropenkrankheiten,' Vol. II.

characterize the disease, neither scientifically nor for practical purposes. It is, in fact, at the present time impossible to determine exactly the morbid entity which really corresponds to the name of dengue. Several diseases are, in one or several particulars, so similar to dengue that it is a matter of serious discussion whether they are closely related to it or even identical with it. The two diseases which have in later years occupied the most prominent position in this discussion are pappataci fever and seven-day fever. Some twenty years ago, when pappataci fever was practically unknown in the scientific world, and seven-day fever had not yet been described, a similar discussion took place with regard to influenza and dengue. But Leichtenstern, and others, pointed out the essential differences between these two diseases, and at the present time it is generally admitted that they are totally different. The discovery of specific micro-organisms (*Bacillus influenzae*, *Micrococcus catarrhalis*) has contributed to make a sharper definition of influenza possible.

With regard to pappataci fever, it would likewise appear that the question has now been finally solved in favour of its separation from dengue. The pathogenic parasite is unknown in both diseases, or, at any rate, unknown in the case of pappataci fever and not known with certainty in that of dengue, but it seems well established that they are transmitted by different insects. The transmission of pappataci fever by sand-flies is considered proved beyond doubt, and the theory of transmission of dengue by mosquitos is supported by very good evidence, although it has not yet met with universal recognition. Different modes of transmission probably mean different specific parasites. It may, therefore, safely be presumed that the two diseases are etiologically different; whether it is true, as has been suggested, that an etiological relationship exists between them, and that their parasites belong to one and the same group, must be left for further researches to decide.

The most important question which at the present time has to be discussed in connection with the nature of dengue

is that of its possible identity with the so-called seven-day fever described by Rogers. This disease is endemic in Calcutta, and is considered by Rogers to be essentially different from dengue, but a number of other authors, writing subsequently to the appearance of Rogers's description, maintain that it is simply an endemic form of dengue. As the pathogenic micro-organism is not known with certainty in any of the two diseases, and as the mode of transmission has not been fully investigated in seven-day fever, the discussion has to deal chiefly with the clinical and epidemiological characters. Rogers has compiled the following table in order to show the differences between dengue and seven-day fever:

	DENGUE	SEVEN-DAY FEVER
Prevalence	At long intervals in epidemic form attacking a large proportion of residents	Annually in sporadic form
Distribution	Specially attacks coast towns, but spreads far inland	Only known near the coast, so far
Race incidence	Europeans and natives equally attacked	Very common in Europeans, comparatively rare in natives
Seasonal incidence ..	Mostly in hot months, but may prevail in cold season (1872)	Prevails in hot and rainy seasons only
Relapses	Very common in same year as first attack	Rare, and not in same year as first attack
Pains	Very severe and breakbone in character	Moderately severe, as in influenza, and not of breakbone character
Joint symptoms	Very common and characteristic	Absent, or only present as slight pain
Convalescence	Very tedious, lasting one to three months, with persistent joint-pains	Rapid. No after joint-pains
Fever	Lasts two or three days, falling to normal with crisis. Occasionally very short secondary rise. Markedly remittent	Five to eight or more days with typical saddle-back remission to 100° to 90° F. only. Otherwise continued in type
Pulse	Rapid	Slow, especially in terminal rise

It is, however, very difficult to bring diagnostic rules in accordance with this table. If we attempt to apply the characters of the table to recently described outbreaks of dengue, the results will be found to be self-contradictory. In some cases Rogers would probably say that the disease in question may not have been dengue at all, but seven-day fever, as he has done in the case of the description by Ashburn and Craig of dengue in the Philippine Islands. But even admitting this possibility, the difficulty has not been solved; it will be found that the disease, as described recently by various authors, cannot be brought under any of the two headings in Rogers's table.

When applying the table, we would naturally consider in the first place the clinical characters. We may take as an example the recent epidemic of so-called dengue in Palestine, described by Canaan and by Masterman, whose descriptions apply more particularly to the disease as it appeared in Jerusalem. It corresponds to dengue in several particulars, according to Rogers's classification. Thus, pains were often—but not always—severe, convalescence was long and tedious, and relapses were common. But, on the other hand, joint symptoms were absent, the pains being described as muscular or tendinous. The fever lasted from three or four to eight or ten days; Canaan observed slight remission of the temperature, and Masterman considers a recrudescence to be typical of many cases, though he is not in possession of detailed observations. Neither of the two authors describes the characters of the pulse. Thus, the clinical characters do not sufficiently characterize this epidemic, but the duration of the fever and the absence of joint symptoms would certainly favour a diagnosis of seven-day fever. The epidemiological characters, on the other hand, correspond closely to those observed in dengue epidemics.

The epidemic in Calcutta in 1912 has been described by Hossack and by Smith; both authors believe in the identity of dengue and seven-day fever, but differ considerably from each other in the descriptions of the symptoms. This lack of accord may be taken to show that the clinical picture

varies considerably, in this as in most other diseases. The fever lasted frequently only three days, according to Hossack, but in Smith's experience its usual duration was five to seven days, and a typical saddle-back type of the temperature curve was of common occurrence. The pulse rate was low, according to Hossack. In Smith's cases, pains (articular?) were a prominent feature. Both authors are strongly of opinion that the disease was dengue, but it must be admitted that it shows perhaps even more resemblance to seven-day fever, according to the symptoms.

If we consider *seriatim* the characters said by Rogers to be of importance for the distinction of seven-day fever from dengue, we will find that the specific value of nearly every one of them has been disputed by one or several authors.

The prevalence is said to be epidemic in dengue, long intervals intervening between two epidemics; seven-day fever is described as endemic. This is contradicted by various Indian authors, who maintain that the two diseases are identical, and especially by Hossack, who points out that it is well known from other infections that a disease may well be at home endemically in a certain locality, and nevertheless occasionally burst forward in epidemic outbreaks. Fooks believes that three-day fever and seven-day fever, which he considers identical with dengue, occur both endemically and epidemically in the Punjab. Pazos is of opinion that dengue is endemic in Cuba, and it is said by Hirsch to be 'not uncommon' in Egypt, Hawaii, India, Senegambia, Bermudas, Honduras, etc., which probably means that it is endemic. Even the most typically epidemic diseases are endemic in one or more localities.

The distribution is said by Rogers to be different, seven-day fever occurring only in coast towns, but dengue also inland. He does not, however, lay much stress on this point, stating that seven-day fever is 'only known near coast, so far.' Later on he mentions, however, that he has received typical seven-day fever charts from cases observed in the Punjab. It would appear that several inland outbreaks—for instance, the one in Jerusalem mentioned above, and

that described from Nowshera, by Wimberley—show more resemblance in the clinical symptoms to seven-day fever than to dengue. It may also be recalled that dengue was by Hirsch and Leichtenstern, and other earlier authors, regarded as a disease of the sea-coasts and river-banks, just as yellow fever was.

Race immunity cannot be considered an absolute characteristic of seven-day fever. Race immunity means practically, as far as it is known from the studies on malaria, yellow fever, and other tropical diseases, immunity acquired through unrecognized infections. Also in dengue has race-immunity—absolute or relative—been mentioned by Stitt and by Vassal. On the other hand, Munro reports a considerable number of cases closely corresponding to Rogers's seven-day fever type in natives of India.

Seasonal prevalence is, so far, perhaps more pronounced in seven-day fever than in dengue, but also the latter disease is frequently said to become extinct spontaneously in Autumn or early Winter. According to Clayton, however, no such thing as seasonal prevalence would appear to exist in seven-day fever, outbreaks having been observed both in Summer, Autumn, Winter and Spring.

Relapses are, according to many authors, not uncommon in dengue; with regard to seven-day fever, Megaw has suffered from this disease twice with a year's interval. That relapses should be very common in the same year as first attack, in dengue, is denied by various observers.

The pains are said by Rogers to be very severe, and of 'break-bone' character in dengue, but moderate in seven-day fever. Severe pains, of course, belong to the classical picture of dengue, but in recent descriptions pains are often said to be moderate. Thus Masterman gives it as a symptom of diagnostic value that the pains are less severe in dengue than in influenza.

Joint symptoms are, according to Rogers, common and characteristic in dengue. In most modern descriptions it is pointed out that the so-called articular pains in dengue are, as a matter of fact, usually juxta-articular, being localized

either to muscles or to tendinous insertions, and stress is laid upon the absence of other signs of affection of the joints, such as swelling, etc.

Convalescence is usually prolonged in dengue, but even this is not a constant feature. In the Fiji outbreak in 1908, Montague observed weakness but a rapid convalescence. Manson mentions that patients may feel quite well after a few days of debility.

The duration of the fever in dengue is by Leichtenstern stated to be three days, but he, as well as other observers, describes a secondary rise, not always very short. More stress is laid upon the constant occurrence of this secondary rise in recent observations, and the fever is even by some authors described as lasting about a week, with a more or less deep remission. In fact, some of the temperature charts published from dengue cases are almost identical with typical charts from Rogers's seven-day fever.

The pulse is usually described as rapid in dengue, but low pulse rates have been observed in dengue, both in India, Australia, the Philippine Islands, and Cuba.

Thus, seven-day fever cannot be differentiated from dengue by any single pathognomonic symptom, and a comparative study of records of the two diseases shows overlapping of the symptoms to an extent which seems very suggestive of their identity. Should they, however, finally prove different, then it is evident that there has been a large amount of mistaken diagnosis, and that the name of dengue has often been applied to cases and outbreaks which were really seven-day fever. On the other hand, assuming their identity, it is quite conceivable that certain features may be fairly constant in one outbreak, and totally or practically absent in another. The same phenomenon occurs in other diseases, as, for instance, in plague and in influenza.

McCarrison's three-day fever seems, according to the observations of Megaw and of Fooks, to be intimately related to seven-day fever, and thus probably also to dengue.

Another disease which must be particularly referred to in this discussion is the six-day fever which Deeks has observed

in Panama. He is inclined to believe that this fever is identical with Rogers's disease, and his description fully supports this view. Thus, to discuss the possible relationship of this disease to dengue would be a repetition of the preceding remarks. Deeks is of opinion that six-day fever is distinct from dengue.

These diseases will have to be specially considered in future investigations on the nature of dengue, and its place in the pathological system. In the case of a number of other diseases a more or less close relationship to dengue has been suggested, from yellow fever to influenza, pappataci fever, and the mildest forms of climatic fever. Perhaps no other diagnosis suggests itself with more frequency to the minds of medical workers in the tropics than that of dengue, as a rule only to be dismissed, however, on account of the absence of classical symptoms. In fact, it would appear that a diagnosis of dengue is seldom made in the absence of an actual outbreak of the infection, even in areas regarded as endemically infected, and the diagnosis is probably never made in mild cases without the simultaneous occurrence of quite typical cases.

History. According to Hirsch, Leichtenstern, and others, the earliest known outbreaks of dengue are those in Batavia, in 1779, and in Cairo in the same year. In the following year an outbreak was observed in Philadelphia. Earlier records of similar epidemics are generally regarded as doubtful. Van der Burg regards also the Philadelphia epidemic of 1780 as doubtful, but states that in the same year outbreaks occurred in the coast lands of Zanzibar, Arabia, Coromandel, Persia, and Tibet (coast land?).

In the following years dengue epidemics occurred in Spain and in South America, and throughout the nineteenth century outbreaks were reported from almost every part of the globe inside the tropics, or where, at least, hot summers occurred. The distribution and sequence of outbreaks were most irregular. Also in this century have epidemics occurred suddenly and unexpectedly in places far distant from earlier foci, and in several places at the same time without any apparent connection.

The first description of dengue was given in 1779 by Bylon (Boylon) in Batavia, and Dzjabarti (Gabarti) in Cairo. The outbreak on the Coromandel coast in 1780 was described by Persin, and that in Philadelphia in the same year by Rush (observations published in 1789).

Many excellent clinical and epidemiological descriptions of dengue have been published in the past century, one of the best being that by Leichtenstern; more recent text-book descriptions are those by Scheube, Manson, van der Burg, Netter, Castellani and Chalmers, Reboul, and others.

In 1902 and 1903 Graham published his observations on the etiology of dengue, and in 1907 Ashburn and Craig published confirmatory evidence on the transmission by means of *Culex fatigans*.

Geographical distribution. Dengue is, and has always been, limited to tropical and sub-tropical countries, with occasional invasions of the temperate zones in exceptionally hot summers. Inside these limits it is decidedly cosmopolitan. The southern European countries, tropical and sub-tropical parts of Asia, Australia, North and South America, and East and West Africa, all have been visited by more or less extensive outbreaks of dengue.

In the case of dengue it is impossible to distinguish with any degree of certainty between endemic areas and areas of epidemic occurrence, as is so readily done in yellow fever. Mild forms of dengue do not attract the attention of the public, nor of medical men, as long as they do not become unduly common, and sporadic cases are probably overlooked in many places. If seven-day fever is identical with dengue, then the principle endemic foci are evidently Calcutta and other parts of India. It is quite possible, probable even, that endemic foci exist in other parts of Asia, and perhaps in various parts of Africa, especially Egypt; endemic prevalence is also looked upon as probable in parts of Australia, of the West Indies, and of the American Continent.

Epidemic outbreaks have been reported in this century: in Europe: Greece;

Asia: Calcutta, Madras, Bombay, Rangoon, Siam, Singapore, Indo-China (Saigon, Tonkin), China (Hong-Kong, Tungkun, Hoyün), Philippine Islands, Japan, Syria, Palestine, South of Persia (Binder-Boucher);

Australia: Queensland, Fiji Islands, Christmas Islands, Hawaii;

America: Cuba, Florida (Tampa), Panama;

Africa: Egypt, Sudan, Natal.

This list is undoubtedly very incomplete, as epidemics of dengue are not reported with the same regularity as those of the more severe, infectious diseases.

Dengue was by earlier authors regarded as a disease exclusively of the coast cities, but it is now known to occur even far inland.

Leichtenstern states that dengue exceptionally, in a particularly hot summer, occurred in the Lebanon up till about 4,500 feet above sea-level, but otherwise it is undoubtedly a disease of the lowlands, higher lying places being protected by their cooler climate. McCarrison has observed in Chitral three-day fever, which with some degree of probability may be considered a form of dengue, at an altitude of about 6,500 feet. The absence of dengue from higher altitudes corresponds to its absence from the temperate zones.

Etiology. The pathogenic organism of dengue is not known with certainty. As early as 1873 and 1886, blood-inhabiting organisms were described by Cunningham and Charles, and by Laughlin, respectively. Later on, Graham, in 1902 and 1903, and Eberle, in 1904, have described intracorpuseular and free elements in the blood, which they regarded as parasites. Graham's observations were confirmed by Ardati in 1910. According to these two authors the parasites are fairly large, motile, unpigmented (Graham), or slightly pigmented (Ardati), not stainable (Graham), or not intensely staining (Ardati).

Graham gives sketch-drawings of the elements observed by himself in 1901, and described in 1902. The elements were roundish, or of a more or less irregular shape, and unpig-

mented. They were quite small during the first twenty-four hours of the disease, but subsequently increased in size, and finally, on about the sixth day, attained almost half the size of an erythrocyte. At this stage they became free, apparently by the rupture of infected blood corpuscles. Degenerated parasites were seen to be taken up by leucocytes. Graham compared his parasite to *Babesia bigemina*. Ardati's description of the bodies, which he believes to be the same as those observed by Graham, is somewhat brief, and entirely unaccompanied by figures, though he states that he has stained the parasites with Giemsa's solution. The parasites are, according to Ardati, similar to malarial parasites, but smaller, less pigmented, usually round, with finer granules, and are less stainable; they stain purple to blue by Giemsa's method. Ardati also observed intracorpuseular motile bodies by dark-ground illumination.

It is possible that the observations of Eberle may be regarded as confirmatory evidence of those of Graham, though his description differs considerably from that given by the latter author. Many other investigators have searched for the dengue parasite, but in vain. It appears, however, very strange that all other observers should have failed to recognize such fairly large and comparatively numerous elements, if constantly present. This circumstance makes it probable that Graham's observations are of no etiological importance, but it is obvious that the question is one which deserves very careful renewed investigation before being dismissed. There is a possibility that not all observers have really dealt with the same disease. It has been suggested, as above mentioned, that the disease so carefully investigated on the Philippine Islands was not dengue, but seven-day fever, and with regard to the most recently obtained negative results of the blood examinations made in Jerusalem by Mühlens, it should be remembered that Mühlens himself was of opinion that he was not dealing with cases of dengue, but of pappataci fever, though the outbreak has been described as one of dengue by Canaan, and by Masterman. Carpenter and Sutton state that they have observed the elements

described by Graham, but are of opinion that they represent a necrobiotic change of the red cell.

The note by Reiche on motile bodies in the blood plasma would appear to need no consideration, as it is much too incomplete and probably deals with well-known blood elements.

According to the experiments of Ashburn and Craig the virus is filterable. These authors obtained positive results by inoculation of blood serum which had been passed through bacterial filters which retained the *Spirillum cholerae* and the *Micrococcus melitensis*. This, of course, with regard to the size of the organism, means only that at least one stage of its evolution is represented by extremely small, though not necessarily invisible, elements; but other stages may possibly be of quite appreciable size.

Although Graham has apparently not succeeded in his search for the parasite of dengue, the other part of his work on etiology, namely, that which deals with mosquito transmission, has been confirmed by several investigators, and accepted by most authors.

Graham first carried out negative experiments. The rooms in several houses in which cases occurred were kept free from mosquitos during from thirteen to seventeen days from the onset of the first case, with the result that no other cases occurred. He then proceeded to transmission experiments, of which the first series were carried out in the infected place, Beirut, on four young men living in houses in which no cases of dengue had occurred previously. Three developed dengue within from four to six days after the application of the infected mosquitos. The fourth, who was not taken ill, was possibly immune, having suffered from a severe attack of dengue twelve years previously. The author, however, admits that the experiments were not absolutely conclusive as long as they were carried out in the infected city. For this reason he subsequently experimented upon two individuals living in a village at an altitude of 3,000 feet, where no cases had previously occurred, and where there were very few mosquitos. Infected mosquitos were carried from

Beirut to the village. Both individuals became infected, after four and five days respectively; they continued to sleep under mosquito nets, and no other cases of dengue occurred in the village. Graham also adduces considerable circumstantial evidence, the most striking being a personal experience. During the epidemic in Beirut, in 1889, the author spent a night in Beirut, and then went up to a mountain cabin, where he slept together with eleven others. There were no mosquitos at the cabin, which was 4,600 feet above sea-level. On the sixth night he developed a severe attack of dengue; none of the other inhabitants of the cabin became infected.

Graham experimented with *Culex fatigans*, but mentions that *Stegomyia fasciata* is also a very common mosquito in Beirut.

Several other observers experimented during the following years with mosquito transmission of dengue, but with negative results, until in 1907 Ashburn and Craig confirmed Graham's work. These authors worked in the Philippine Islands, and had at their disposal a rather unfortunate material, as the larger number of the individuals experimented upon were immune, as is shown by the negative result of subsequent injections of blood from dengue patients. Thus, the authors consider only four experiments as being of any value; of these, a positive result was obtained in one, but this percentage is by the authors considered much too low, as they do not feel certain that the other individuals were bitten by the mosquitos. Ashburn and Craig also experimented with *Culex fatigans*, but leave the question open whether other mosquitos might as well serve as transmitters. These investigators experimented, as far as it can be gathered from their report, at Fort McKinley, which was heavily infected at that time.

It is unquestionable that Graham first established the mosquito transmission theory in dengue, and supported it by very good evidence. It is unfortunate that the account of his experiments is somewhat summary, but it appears that in the last two experiments sufficient safeguards were taken against

the possibility of casual infection. In fact, it would appear that he proved his theory as far as absolute proof is obtainable in such matters. It is, however, remarkable how little attention has been paid to Graham's work, even in the literature from recent years.

Graham is of opinion that the dengue parasite undergoes a development in the mosquito, and states that he has produced infection by injecting an emulsion of salivary glands of a mosquito infected twenty-seven days previously. He gives no details with regard to the intervening period in the transmission experiments, but evidently believes the evolution to be of very short duration, as he describes 'spores' in the salivary glands of mosquitos forty-eight hours after the infecting bite. Ashburn and Craig are inclined to the belief that the transmission is a purely mechanical act; if the parasite should undergo an evolution in the body of the mosquito it must be a very short one, as the intervening period in their one positive experiment was only of two days' duration.

The distribution of dengue would correspond well to the universal prevalence of *C. fatigans* in warmer countries, but equally well to that of *Stegomyia fasciata*, and it has been suggested by Legendre that the latter mosquito might be the most important carrier in dengue.

Epidemiology and general pathology. Most of the questions belonging to this section have already been discussed under the foregoing headings. The life habits of *C. fatigans* explain the seasonal prevalence of dengue, as well as its geographical distribution, and also the observation which has been reported by various authors that infection seems to take place chiefly or exclusively during the night.

The explosive character of epidemic outbreaks which has always been regarded as a peculiar feature of dengue, is not exactly what we would expect in an insect-borne disease, but it might be explained, where mosquitos are abundant, if the transmission is of a mechanical nature. Many epidemics have been remarkably extensive, almost the whole population of a town being attacked.

The peculiar way of spreading from barrack to barrack, which has been described by Ashburn and Craig in the case of the Fort McKinley outbreak, would correspond well to transmission by insects.

Nothing definite is known about the infective period of the blood in dengue. By some authors the later period of the disease is considered the most dangerous with regard to transmission.

Considering the lack of knowledge of the parasite, and also of the anatomical lesions, it is only natural that nothing is known with regard to the mechanism of the production of the symptoms.

Immunity. Some authors are of opinion that an attack of dengue leaves little or no immunity, whilst others speak of a well-established and more or less persistent immunity. Repeated attacks during one and the same outbreak have often been reported; on the other hand, there seems to be reliable evidence which shows that one attack has protected an individual, both during the same and later outbreaks, even for many years.

Pathological lesions. No specific lesions have been described. Uncomplicated cases are apparently never fatal, and most of the lesions observed on post-mortem examination may have been due to secondary infections. Van der Burg, however, seems to regard serous exudations in subcutaneous tissues, in joints, pericardium, and brain, and softening of the heart muscle, as phenomena essentially belonging to dengue.

Incubation. According to clinical observation the length of the incubation period varies from a few hours to several weeks. Pülle gives, from the observation of a sharply circumscribed outbreak, 10 hours as a minimum and 39 days as a maximum period of incubation. The Brisbane report gives apparently reliable data from several cases; in a few the incubation period seems to have been less than 48 hours and in one case less than 24 hours; on the other hand, in one case it must have been at least three days. In Graham's experiments the incubation was from three to six days, and

in those of Ashburn and Craig it varied between two and five days, the average being three days and fourteen hours.

Symptomatology. Considerable variation is observed, with regard to the individual symptoms, during one and the same outbreak and, even more, when comparing different epidemics.

Most authorities describe a sudden onset, often with a chill or rigor, but a more gradual beginning is also observed, either in isolated cases, or in certain outbreaks. Prodromal symptoms are not common, but in some cases headache and general malaise precede the actual declaration of the illness by several hours or a whole day. One experimental case, published by Ashburn and Craig, is of considerable interest; the patient had a rise of temperature before he complained of any symptom.

There is always fever from the beginning, but the first symptom which attracts the attention of the patient is often pain, which may be so intense and sudden that the patient is interrupted in his work and unable to move. This 'dramatic' onset, which appears to have been not uncommon in some earlier epidemics, is, however, rarely mentioned by recent authors. The pain may start in any part of the body, usually in one of the extremities, but it soon spreads and febrile symptoms soon develop.

The temperature rises quickly to about 39° C. (102° F.), but may rise considerably higher, already in this period. The fever remains more or less continuous, or with slight morning remissions, for one, two or three days; then the temperature usually falls to normal, or nearly so, and becomes stationary for two or three days. A secondary rise takes place on the fourth, fifth, or sixth day, this phase of the fever lasting for one or several days, or only for a few hours; secondary fever of more than a few days' duration is probably a sign of some complication or other. In some cases the initial fever is higher than the secondary one; in other cases the inverse condition is observed. Hyperpyrexia has been observed, exceeding 42° C. ($108-109^{\circ}$ F).

This recurrent form probably represents the typical fever

in dengue, but great variations occur. The fever may last a few days only; on the other hand, it may be continuous, or more or less remittent, for a week; the so-called 'saddle-back' type, with initial and secondary fever of about the same height and duration, and a fairly deep intervening remission, is not uncommon. Short fevers are easily explained as abortive forms, which may occur in any infection, but the more continuous forms cannot be fully explained, as long as the pathological physiology of dengue is so imperfectly understood. The fall of the temperature generally takes the form of a lysis, but a sudden, critical drop may occur, accompanied by profuse sweating.

The pulse is variously described; a somewhat low pulse rate is probably the rule, slightly lower than one would expect, considering the height of the temperature—a condition similar to that in typhoid fever; the disproportion is not so pronounced, nor so frequent as in yellow fever. High pulse rates are also recorded, and in some outbreaks they seem to have been prevalent. In the convalescent period low pulse rates are common, sometimes down to 48 per minute, or even less. The pulse is usually fairly strong and regular, often described as tense, but may be weak and soft, especially in a late stage of the disease, or during convalescence.

Other febrile symptoms are often pronounced, such as headache, congestion of the face, and uneasiness. The headache is often orbital, and increased by movements of the eyeballs. The conjunctivae are hyperaemic, both on the eyeballs and on the eyelids; injection of the lower palpebral conjunctivae has been considered pathognomonic in dengue. Photophobia is common.

General nervous symptoms are not prominent, except considerable depression. Insomnia occurs and delirium, but the latter is very rare.

Muscular pains are very common, and so are pains which are commonly referred to as articular; but most recent observers are agreed that these pains are usually juxta-articular, being localized either in the adjoining muscles or

in tendinous insertions. Exudation and other objective signs of inflammation of joints are decidedly rare, and muscular swellings have apparently not been described.

The pains, whether muscular, tendino-periosteal, or articular, may occur in any part of the body. Backache is probably constant, and one or more of the extremities are usually affected. The pains are often extremely severe, partially or completely immobilizing the patient. Intense suffering is sometimes experienced by the combination of severe pains with insomnia and debility.

Cutaneous phenomena are common and important. An initial rash is usually observed, but has apparently been absent, not only in single cases but in several outbreaks. It is most frequently described as a diffuse hyperaemia, but is sometimes said to be measles-like. It is visible especially on the face and extremities. It soon fades and is probably often overlooked. At the time of the secondary rise of temperature a papular, scarlatiniform or measles-like rash appears, which is accompanied by itching and followed by desquamation. More exceptionally it presents the characters of an urticarial eruption, and in very rare cases it may be haemorrhagic, purpura-like. The rash is very irregularly distributed, and may be limited to small, circumscribed patches. It remains visible for one or two days. Desquamation may be very scanty, but also occasionally as pronounced as in well-characterized cases of scarlatina. Cutaneous hyperaesthesia is seen in some cases, especially during convalescence.

The circulatory system is not severely affected. The characters of the pulse have already been discussed. Haemorrhages may occur, but are rare, except epistaxis which is fairly common; other haemorrhages are haematemesis, haemoptysis, and haematuria, which have been observed in a few cases. If an attack of dengue occurs at the time of the menstrual bleeding, this may be increased; otherwise, spontaneous metrorrhagia may occur. Cerebral haemorrhage has been reported in one case by the Brisbane Commission; in another case they observed both subcutaneous haemorrhage and haemorrhage into the ankle-joint.

The blood shows little alteration, except in the leucocyte count. A slight, or well-pronounced, leucopenia is the rule and, perhaps, a constant character. Differential counts which have been published by Ashburn and Craig and others, show a numerical reduction of the polymorphonuclear leucocytes, down to about fifty, or even forty per cent., and an increase of the large mononuclears and lymphocytes, the latter predominating. Some authors maintain that the leucocyte formula remains essentially the same throughout the disease, but others are of opinion that considerable variations occur. Stitt has found an initial mononuclear increase (large mononuclears and transitionals), which, later on, is substituted by an increase of the small lymphocytes.* The polymorphonuclear decrease is observed already on the first day, and is regarded by Ashburn and Craig and by Stitt as being of considerable diagnostic value. The percentage of eosinophiles is either normal or reduced.†

The respiratory apparatus is but little affected. Pneumonia is exceedingly rare, and bronchitis seems to have been rare in most outbreaks, but fairly common in a few; when present, it is usually mild.

Also pharyngo-tonsillitis has been described, but is by most authors looked upon as rare and of little consequence.

Enlargement of the peripheral lymph nodules has in several outbreaks been fairly common, and is mentioned in many reports as occurring in a certain number of cases. The spleen is not enlarged. Enlarged lymph-nodules formed the most striking feature in an outbreak among troops in Natal, reported by Beveridge, but the author does not regard the diagnosis of dengue as beyond doubt; it is also mentioned that the lymph-adenitis might be a complication.

The digestive tract is always affected, but seldom severely. The tongue is coated with a whitish fur, but tip and edges often remain red, and in many cases the tongue cleans itself

* According to his own more recent observations, Stitt lays little stress upon the distinction between two stages; he now states that the proportion between large mononuclears and lymphocytes varies irregularly.

† Harnett has found a post-febrile eosinophilia which he regards as characteristic.

later on in the disease. Nausea is constant, and vomiting not uncommon; epigastric pain is often observed, and abdominal pain may occur, even simulating appendicitis. Cazamian describes a case of appendicitis as a complication to dengue and suggests that dengue might be of a certain etiological importance in appendicitis. Constipation is the rule, but it may be followed later on in the disease by diarrhoea, sometimes with dysenteriform characters. Slight enlargement of the liver and slight jaundice have been described, but are quite exceptional. Anorexia is common, and may persist for some time after recovery.

The kidneys are seldom affected. Albuminuria occurs in a certain number of cases, the frequency varying very considerably according to the authors; the amount of albumin found is usually very small, and soon disappears. In a few cases acute, even fatal nephritis has been observed; when not fatal, the symptoms have disappeared after a few weeks. Haematuria has been observed in a few cases.

Diazo-reaction is seldom mentioned; when tested for, it has been found negative.

Complications are rare in dengue. The following have been reported, mostly in isolated cases: pneumonia, pleuritis, parotitis, orchitis, keratitis, iritis, chorioiditis, spondylitis, myelitis, boils, carbuncles, and ulcerous stomatitis. A tendency to miscarriage and premature labour, so common in infectious diseases, is also mentioned by some authors, but others deny that dengue should have any influence upon pregnancy.

Convalescence is described by some authors as rapid and easy, but by the majority as long and tedious. Some of the complications mentioned above are apt to prolong the illness and convalescence, but, apart from that, considerable depression and sometimes long persistent pains are said to be common. Also insomnia may persist for months after the actual recovery from an attack of dengue.

The course of an attack of dengue is often divided into periods: initial fever, intermittent stage, secondary fever, stage of desquamation, and convalescence. It must, how-

ever, be remembered that these stages are by no means always well defined, and that one or more may be entirely missing.

The most typical attacks usually occur in vigorous adults, whilst mild and atypical cases are often seen in children.

Mortality. In most outbreaks the mortality has been very low. Various reports give mortalities of 1 out of 4,000, 7,000, or 10,000 cases, and in several epidemics no fatal cases are recorded. But in a few outbreaks higher mortalities have been observed, as 4 per 1000, or even up till 10 or 20 per 1000.

Most fatal cases have occurred in children, or in old or weakly individuals. It seems probable that dengue is never fatal *per se*; complications have generally been found to be responsible for the fatal issue.

Prognosis. The prognosis *quoad vitam* seems to be invariably good in healthy and strong adults. In the case of children, or when weak, sickly, or aged individuals are attacked, considerable care must be taken in order to avoid complications.

Final recovery can also safely be predicted, but the possibility of a long and tedious recovery must not be lost sight of; no speedy return to work can be promised.

Diagnosis. In a typical case of dengue the diagnosis should be easy enough, and in some other cases it will be greatly facilitated by the presence of an epidemic. In the latter event there is, apparently, often a tendency to include too many cases, to diagnose all minor ailments as dengue. On the other hand, the diagnosis of the first cases in an epidemic outbreak, or of atypical cases in an endemic area may be a matter of considerable difficulty.

The symptoms upon which particular stress should be laid from a diagnostic point of view are the curve of temperature, especially when the recurrent type is well marked, the rashes, and the character of the pains. The conditions of the pulse are apparently too inconstant to be of considerable diagnostic value. More characteristic than the individual symptoms is the combined picture of a short fever with muscle or joint symptoms, unaccompanied by inflammatory phenomena, with

rash and desquamation, but without, or with only slightly marked throat affection. Many diseases might be discussed in connection with the differential diagnosis of dengue, from sunstroke to acute polyarthritis or scarlet fever, but the diseases which will most frequently give rise to difficulties are: influenza, pappataci fever, yellow fever, malaria, and 'climatic fevers.'

Dengue is differentiated from influenza chiefly by the absence of catarrhal symptoms, the more marked pains and their particular characters, and by the seasonal incidence. The absence of the influenza-bacillus is an indication of some importance, but not decisive, as we know that 'influenza' is not infrequently produced by other organisms, and also that the specific bacillus may be missed, even in cases of true bacillary influenza. Leucopenia and low percentage of polymorphonuclear leucocytes are also symptoms of diagnostic value, as different conditions obtain in influenza.

Pappataci fever may be very similar to dengue, but is recognized by the shorter fever, and by the absence of 'juxta-articular' pains, and of rashes.

Only very mild cases of yellow fever could be mistaken for dengue. In such cases the examination of the urine is of particular value, as albumin is as common in yellow fever as it is uncommon in dengue.

Malaria is, as a rule, distinguished by the demonstration of the specific parasite, but it must always be borne in mind that a considerable number of individuals in malarious countries may harbour malarial parasites, without actually suffering from malarial fever.

With regard to the diagnosis of 'climatic fevers' the question is simply one of avoiding this diagnosis by sharper differentiation.

Until the parasitological question has been finally solved in dengue, there will probably always remain some cases in which an absolutely certain diagnosis cannot be arrived at by clinical means, or even by considering also the geographical, climatic, and mosquito conditions.

Treatment. No specific treatment is known so far in the

case of dengue. There is, however, a wide scope for medical therapeutics, as symptomatic treatment can greatly relieve the patients.

Rest in bed is, of course, necessary during the whole course of the illness. The sick-room should be well ventilated, but good care must be taken not to expose the patient to draught.

During the acute stage most patients will probably refuse food, but as soon as possible liquid food should be given, and during convalescence good nourishment is essential.

Quinine is often given, but seems to be of little effect.

The constipation must be combated with mild purgatives.

Sodium bicarbonate is recommended by van der Burg against the gastric symptoms.

Phenacetin, salipyrin, aspirin, or similar compounds are useful in combating the pains, but seem to have little influence upon the course of the disease. Some authors have warned against the indiscriminate use of these products, on account of the tendency to renal irritation which is present, though not very marked, in dengue. In the case of very intense pains it might be necessary to add small doses of codein, or even morphia, to the above compounds. Fifty centigrammes of salipyrin with one centigramme of codein, repeated several times a day, have proved a useful medication in similar cases. Local applications, as hot fomentations, may become necessary.

Insomnia may require the administration of bromides, sulphonal, or other narcotics.

Prophylaxis. As dengue is not a dangerous disease, protection against it by means of quarantine measures would hardly be justifiable. Nor can it be expected that such vigorous campaigns should be started against it as against yellow fever. But the great inconveniences produced in a community by a severe dengue epidemic make it desirable that prophylactic measures should be taken as far as practicable. They should be similar to anti-mosquito measures in general, and especially to those to be taken in the case of yellow fever outbreaks. Thus, destruction of larvae, fumigation, and screening would have to be

considered. According to E. H. Ross, dengue disappeared from Port Said as a consequence of the anti-mosquito measures which were part of a general sanitary scheme. Numerous instances are on record, showing that mosquito-free places have kept free from dengue-infection at times when neighbouring places and surrounding countries have been severely infected.

If *C. fatigans* really should prove to be the only transmitter, then mechanical protection ought to result easier in the case of dengue than in yellow fever, as this species is said to be an exclusively night-biting mosquito.

If sandflies are also concerned, then, of course, the same difficulties will have to be faced as in the case of pappataci fever.



